IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Re:	Applicants:	Hiroyuki ABURATANI, et al.
	Application No.:	10/526,508
	Filing Date:	August 9, 2005
	For:	**ANTIBODY AGAINST SECRETED N-TERMINAL PEPTIDE OF GPC3 PRESENT IN BLOOD OR C-TERMINAL PEPTIDE OF GPC3**
	Examiner:	Minh Tam Davis
	Art Unit:	1642
	Confirmation No.:	4237

DECLARATION OF INVENTOR
HIROYUKI ABURATANI UNDER 37 C.F.R. § 1.132

S I R:

I, Hiroyuki Aburatani, declare as follows:

1. I am a Professor and am employed at the Genome Science Division, Research Center for Advanced Science and Technology at the University of Tokyo. My major field of expertise is in genome science.

2. I hold an M.D. which I received in 1980 from the University of Tokyo, Tokyo, Japan, and hold a PH.D. which I received in 1988 from the University of Tokyo, Tokyo, Japan, Ph.D. in Medicine. My work experience is as follows:

1980-1981 Internship in Internal Medicine, University of Tokyo

1981-1982 Clinical fellow, Toshiba Central Hospital, Tokyo

1982-1983 Clinical fellow, Tokyo Metropolitan Komagome Hospital, Tokyo

1983-1988 Clinical Research Fellow, Third Department of Internal medicine, University of Tokyo

1988-1991 Assistant professor, Third Department of Internal medicine, University of Tokyo

1988-1994 Visiting Scientist, Center for Cancer Research, MIT, Cambridge, MA, USA

1995-1999 Assistant professor, Third Department of Internal medicine, University of Tokyo

1999-2001 Associate Professor, Genome Science Division, Research Center for Advanced Science and Technology, University of Tokyo

2001-present Professor, Genome Science Division, Research Center for Advanced Science and

Technology, University of Tokyo (as of September 1st)

2002-2005 Visiting professor, Kumamoto University.

3. I am a Council Member in the Japanese Cancer Society, the Japanese Society for Gastroenterological Carcinogenesis and the Japanese Society of Human Genetics and am a Society member in: the American Society for Human Genetics; the American Society for Cancer Research, the Japan Internal Medicine Society, the Japanese Cancer Society, the Japan Molecular Biology Society, the Japan Bioinformatics Society, the Japanese Society for Gastroenterological Carcinogenesis and the Japanese Society for Human Genetics

3. I am an inventor of the above-identified patent application, Serial No. 10/526,508, filed August 9, 2005, entitled ANTIBODY AGAINST SECRETED N-TERMINAL PEPTIDE OF GPC3 PRESENT IN BLOOD OR C-TERMINAL PEPTIDE OF GPC3.

4. I submit this declaration in accordance with 37 CFR § 1.132 in response to the Advisory Action from the U.S. Patent and Trademark office dated April 6, 2010 with regard to the above-identified patent application.

5. I understand that, in the final Office Action dated October 26, 2009, the Examiner rejected Claims 1 to 3, 5 to 8, 16 to 18, and 21 to 23 under 35 U.S.C. § 112, first paragraph, allegedly for lack of enablement for a method for diagnosing GPC3 protein expressing cancer, including hepatic cancer.

6. I have reviewed the final Office Action dated October 26, 2009, the Advisory Action dated April 6, 2010 and the present claims.

7. In the Advisory Opinion, the Examiner argued that other than for melanoma "one cannot predict the claimed method would be successful in detecting the presence of any cancer that overexpresses GPC3, including hepatic cancer, when based on an increase in the level of GPC3 in blood, serum or plasma as compared to that of healthy individuals". The Examiner asserted two reasons:

1) the claimed method is non-specific for hepatic cancer, and cannot distinguish suspected hepatic cancer from liver cirrhosis, because the level of soluble GPC3 in blood or serum or plasma is increased in both hepatic cancer patients and liver cirrhosis as compared to soluble GPC3 in blood or serum or plasma of healthy individual, in view of the teaching of Hippo et al, of record.

2) a single cancer, melanoma, that can be detected with the claimed method, one cannot predict there exist any other cancers that overexpress the protein GPC3 in blood,serum or plasma. The Examiner specifically contends that one cannot predict whether cancers such as lung cancer, colon cancer, mammary cancer, prostate cancer and lymphomas overexpress the protein GPC3 in blood, serum or plasma, when based solely on the data from cancer cell lines in culture, due to the well known cell culture artifacts, in view of the teaching of Drexler et al, Tian et al, Van Dyke et al and Kunkel et al.

8. I respectfully disagree with the Examiner's position in this regard and explain my reasoning below.

9. In my experience, 100% accuracy is neither required, nor expected, for any cancer markers. Those skilled in the art well recognize that existent traditional cancer markers provide false positives and that cancer markers used for diagnosing cancer frequently show positive values in benign disease. As no cancer markers show 100% specificity (at least none of which I am aware), physicians, by necessity, understand how to make diagnostic decisions while keeping in mind the nature of a specific tumor marker.

10. Support for my position is found in the widely used cancer marker AFP which is used as a cancer marker for hepatocellular carcinoma ("HCC") but is known to show positive values in Liver Cirrhosis ("LC") or hepatitis. Support can also be found in the Hippo et al. reference (which I understand is of record) which shows ROC (receiver-operating characteristic) curve

analysis of sGPC3 and AFP in Figure D. As seen in the Hippo et al. reference, when 43 cases treated with surgery were confined to 32 cases with relatively early stage HCC (7 cases with WD HCC and 25 cases with MD HCC), the calculated area under the ROC curve for sGPC3 and AFP were 0.726 and 0.710, respectively, indicating that sGPC3 is superior to AFP (Figure 3D). The sensitivity of sGPC3 and AFP for the diagnosis of WD HCC and MD HCC was 50% and 47% respectively. Moreover, combination measurement of both markers in WD HCC and MD HCC also markedly improved sensitivity to 72%. These results clearly demonstrate the utility of sGPC3 as a cancer marker for HCC.

11. Further support for my opinion that 100% accuracy is not required for cancer markers can be found in the articles attached hereto as Exhibit Nos. 7-15. As demonstrated in the references set forth in Exhibits 7-10, even widely-used tumor markers often provide false positives and physicians understand that these markers sometimes show false positives but are still useful in diagnosis of cancer. For example, it can be seen in Exhibit 7 that AFP, a traditional HCC marker, shows a false positive in liver cirrhosis cases (see Exhibit 7, Figs. 1 and 2) and that a new marker AFP-L3, with alleged improved performance, still shows false positives. Similarly, Exhibit 8 demonstrates that AFP can show a false positive in liver cirrhosis cases (see Exhibit 8 at Fig. 2, Table 3). In Exhibits 9 and 10, PSA, a traditional tumor marker, is shown to give false positives (see Exhibit 9 at Figs. 1 and 2 and Exhibit 10 at p. 154, right column, lower paragraph).

12. As evidenced in Exhibits 11-15, when using widely-used tumor markers known to often provide false positives, those of skill in the art know how to select a cut-off point to obtain a desirable combination of the specificity and sensitivity. A brief discussion of the teachings of these references is set forth below.

13. In Exhibit 11, the specificity and sensitivity of PSA are shown in Figure 1 to demonstrate a trade-off relationship with each other. Exhibit 11 teaches that one of skill in the art is able to select an appropriate cut-off level to obtain desirable specificity and sensitivity. It is of note that Exhibit 11 was published in 2001 just after the priority date of the present application and therefore shows the state of the art as of the priority date.

14. Exhibit 12 shows that false positives for the marker CA 242 are found in normal subjects and in a benign disorder and that an average +/-2 standard deviation of normal subjects or 95 percentile of normal subjects can be used as a criterion value. (See, e.g. Exhibit 12, p. 217, left column, Fig 2).

15. Exhibit 13 again teaches that the cut-off levels for several tumor markers may be set in view of the balance of specificity and sensitivity (See Exhibit 13, Table 1, and discussion of the same).

16. In Exhibit 14, specificity was examined under different cut-off points (see Exhibit 14, Table II) with the distribution of tumor and benign disorder demonstrating the existence of false positives (Exhibit 14, Fig 1). Exhibit 14 also teaches setting the cut-off value via the 95%-specificity approach (Exhibit 14, Table III).

17. Exhibit 15 teaches setting the cut off value of the marker based on the ROC curve (see Exhibit 15 at p. 2921, left column). Exhibit 15 explicitly states that "[n]one of these tests has 100% accuracy" (see Exhibit 15, p. 2921, left column, last paragraph).

18. Based on the evidence of Exhibits 11-15, it is clear that one of skill in the art would understand how to practice the claimed invention even though the method does not provide 100% specificity. In fact, those skilled in the art would recognize it unreasonable to require 100 % specificity to meet the enablement requirement in any type of diagnostic methods.

19. With regard to the Examiner's second reason in support of the rejection, I refer to Exhibits 1-6, which show the expression of Gypican 3 in other types of cancer, including gastric carcinoma (Exhibit 1), thyroid cancer (Exhibit 2), chromophobe renal cell carcinoma (Exhibit 3), clear cell adenocarcinoma of ovary (Exhibit 4), lung squamous cell carcinoma (Exhibit 5) and germ cell tumors or ovary and testis (Exhibit 6). In my opinion, these articles clearly demonstrate that the present invention is also enabled with respect to cancers other than melanoma.

20. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true. Further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued hereon.

Date: September 27, 2010

Hiroyuki Aburatani